SUPPORT FOR THE AMENDMENTS

Figure 6 shows overlaid PXRD spectra of polymorphic forms A, B and C, with arrows above the spectrum of Form A (the upper trace) indicating where to find peaks of forms B and C, if present. One can see from the upper trace that this sample is substantially free of forms B and C, determined by the absence of peaks from polymorphs B and C at around 9° 2-theta. No new matter has been added.

REMARKS

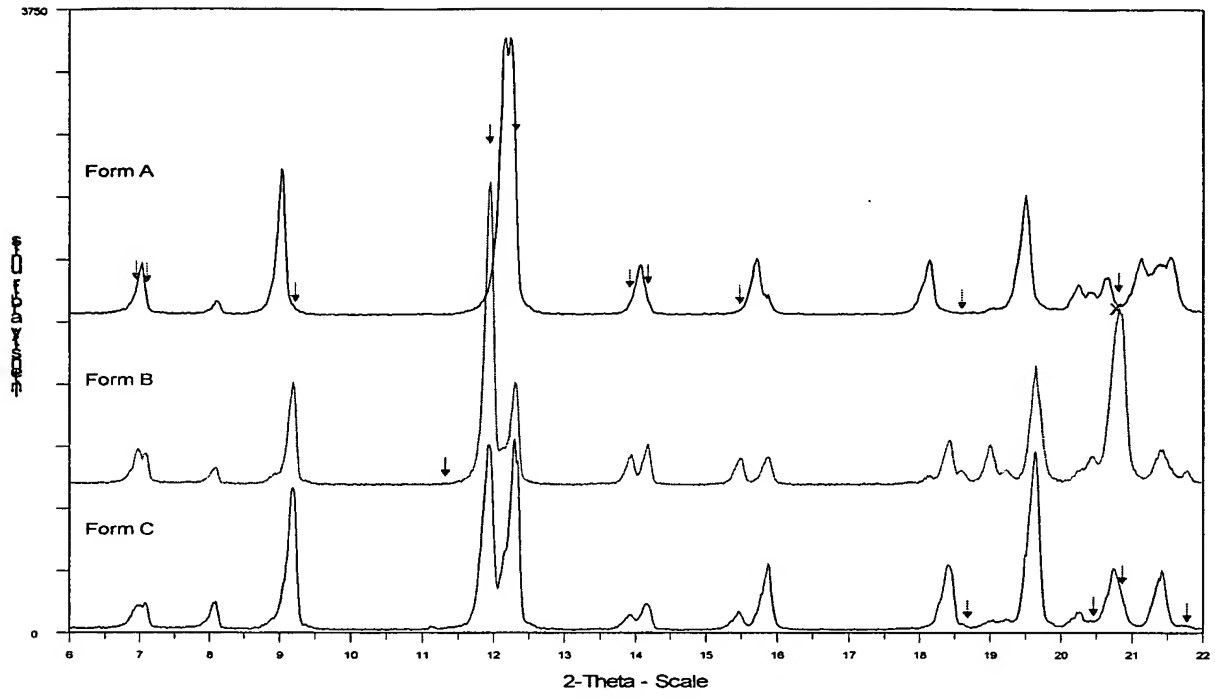
Claims 1 – 3, 5 – 9 and 11 remain active. Undersigned counsel thanks Examiner Oh for an interview held on November 16, 2004, which is summarized below.

The present invention relates to a pharmaceutical composition containing crystals of compound (1) in polymorphic Form A, and substantially free of polymorphic forms B and C.

Claims 1 – 7 stand rejected under 35 USC 112, first paragraph for lack of enablement on grounds that there is no teaching which would enable one of skill in the art to practice the invention as claimed. This rejection is respectfully traversed.

The application describes in Example 4 how to obtain crystals of polymorphic form A substantially free of forms B and C. Three different PXRD spectra, of the separated polymorphs A, B and C, are all shown in Fig. 6, which is reproduced below. A person of skill in the art could readily identify the different crystal products by using the same kind of PXRD analysis, which is discussed in Example 10 of the specification.

The desired polymorph (Form A) could then be formulated into tablets by a person of skill using, for example, the dry granulation method disclosed in Example 8. This formulation process would not be expected to cause any change in the polymorphic structure, and the applicants confirm that it does not do so.



The Examiner noted that the there is no information in the specification about the x-ray pattern of Form A *in the tablet or capsule* (OA page 3, lines 8 – 9). However, the applicants have performed x-ray powder diffraction experiments on both the powder and the tablet. These spectra confirm that, within the limits of the technique, no change in polymorphic form occurred by placing Form A in a tablet. Thus, a sample of Form A, whether in a tablet or capsule would be expected to retain the high solubility behavior shown in Example 5 of the specification.

The data in Example 5 are reproduced below for convenience. At the interview Examiner Oh took the position that the starting material in the experiment may have been a mixture of different polymorphs. And if so, the phrase "solubility was calculated by subtractive means" could imply that all of the dissolved material was merely assumed to be Form A. However, that is not how the experiments were conducted.

Two separate lots of essentially pure Form A and Form B, as determined by XRPD (designated "Desired polymorph form V (form A)" and "Undesired monoclinic polymorph," respectively) were tested for solubility characteristics. No mixtures were tested.

In these experiments the separate compounds were suspended in ethanol/water (2:1, 100 ml) and stirred for one hour at either 22°C, 30°C, or 40°C. Each suspension was then filtered and the remaining solids were dried in a vacuum oven at room temperature overnight to give an insoluble material. The solubility of each compound was calculated by subtractive means based on the recovered solids.

Temperature	Desired polymorphic form V (Form A)	Undesired monoclinic polymorph (Form B)
22 °C	6.7g/L	3.4 g/L
30 °C	15.7g/L	6.1 g/L
40 °C	46g/L	17.2 g/L

Under these conditions polymorph A was far more soluble. For instance, at 30 °C more than 2.5 times as much of Form A dissolved as Form B (15.7 g/ 6.1 g = 2.57). This high solubility behavior is advantageous in the manufacture and administration of a solid pharmaceutical composition.

Accordingly, a person of skill in the art can make and use the claimed invention and the rejection for lack of enablement should be withdrawn.

Formal drawings with clear numbers addressing the objection to the drawings, on page 2 of the Office Action, will be submitted as soon as they become available.

Claims 1, 2, 4, 5, 8 10 and 11 – 12 are rejected under 35 USC 102(b) over Ohashi et al., for inherent disclosure of Form A, and under 35 USC 103(a) for obviousness over Ohashi et al in view of Grant and Hack's Chemical Dictionary.)

Ohashi et al. discloses the compound of interest, but is silent about crystallizing it into different polymorphic forms. There is no clue as to whether one form might have an advantage of *any* kind over another, or whether different polymorphs might even be available. In order to prove that a reference inherently discloses a composition one must point to a process or description of the material which *inevitably* results in the claimed product, including every

limitation of the claim. Nothing in Ohashi et al. even suggest the possibility the crystals can have three different polymorphic forms. Accordingly, it does not inherently disclose the claimed invention.

With regard to obviousness, again Ohashi et al. fails to give any reason to suspect that the compound could be crystallized into three different polymorphs, or what any of the physical properties of various forms might be even if they existed. The Chemical Dictionary reference does not supply any such motivation either.

It is not proper to reject an invention for obviousness using hindsight and applicants' own disclosure against him, as the Examiner has done on page 8, last paragraph, in arguing essentially that different polymorphs are sometimes observed in solid compounds, so a person of skill in the art would be motivated to search for them and select the best for any given purpose.

The prior art must contain a specific motivation to do what the applicant has done. It is not enough to say that routine exploration of any compound's properties *alone* is enough to establish a prima facie case of obviousness. Accordingly, the present invention would not have been obvious within the meaning of 35 USC 103(a).

Claims 1, 3, 4, 8, 10 and 12 are rejected under 35 USC 112, second paragraph, as being indefinite.

Claims 1, 8 12: The phrase "substantially free of other polymorphic forms" has been changed to "substantially free of polymorphic forms B and C" in claims 1 and 8. This phrase is clearly definite. Claim 12 has been cancelled without disclaimer.

Claim 3 has been amended to recite "pharmaceutical composition" to account for the tablet or capsule formulation.

Claims 4 has been cancelled without disclaimer. Claim 5 now recites: "The pharmaceutical composition of claim 1, wherein the compound of formula (1) exhibits no PXRD peaks of polymorphic forms B and C at about 9° 2-theta." This language is definite because one can use Fig. 6 as a standard for the appearance of PXRD peaks of polymorphic forms B and C at about 9° 2-theta.

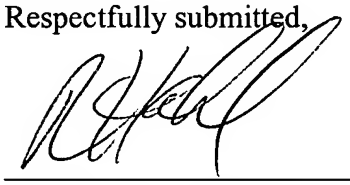
Claims 3 and 7 now contain antecedent basis for a tablet or capsule.

Claims 4 and 10 have been cancelled without disclaimer.

AUTHORIZATION

Applicants believe there is no additional fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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